Growth Hormone Stimulates Protein Synthesis during Hypocaloric Parenteral Nutrition

Role of Hormonal-Substrate Environment

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The influence of growth hormone (GH) on protein metabolism and fuel utilization was investigated in eight paired studies of normal volunteers. GH (10 mg) was given daily during one period, and saline was injected during control studies. For 6 days, subjects received parenteral nutrition that provided adequate dietary nitrogen, vitamin, and minerals, but energy intake varied to provide 30–100% of requirements. On Day 7, the feedings were discontinued and an oral glucose load (100 g) was administered. The level of energy intake did not markedly influence the actions of GH. During nutrient infusions, GH caused positive nitrogen balance (1.0 ± 0.3 g/m^2/day *vs.* −1.2 ± 0.3 in controls, $p < 0.001$) and increased protein synthesis (16.8 ± 0.7 g N/m^2/day *vs.* 13.9 ± 0.8, $p < 0.01$). No change in the rate of protein breakdown or excretion of 3-methylhistidine occurred. GH was associated with an increase in insulin and insulin-like growth factor-I concentrations (IGF-I, 9.1 ± 0.6 IU/ml *vs.* 3.3 ± 0.5, $p < 0.001$). After discontinuation of the parenteral nutrition and administration of the oral glucose load, glucose concentrations tended to be higher after GH; however, despite a two- to threefold increase in insulin response, muscle glucose uptake was attenuated (1.10 ± 0.19 g/kg forearm *vs.* 1.64 ± 0.30 in controls, $p < 0.05$). Compared with control conditions, GH appeared to attenuate the increase in amino acid nitrogen efflux from muscle after the administration of oral glucose. These data demonstrate that the protein anabolic effect of GH, which occurs even during hypocaloric feedings, is related to multiple mechanisms that favor protein synthesis. These include the increase in plasma concentrations of GH, insulin, IGF-I and fat utilization. GH administration results in a hormonal-substrate environment that favors nitrogen retention and protein synthesis. GH may be beneficial in promoting protein synthesis in surgical patients, particularly in association with hypocaloric glucose infusions that allow utilization of body fat as an energy source.

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GROWTH HORMONE (GH) is a potent anabolic agent which has profound effects on the metabolism of protein, carbohydrate, and lipid. Because GH has, until recently, been in short supply, many of the metabolic effects that occur after long-term GH administration in humans are poorly understood or unknown. The development of recombinant DNA techniques has allowed large-scale production of GH, making it available for broad clinical use. It is therefore important to examine the metabolic actions and potential clinical uses of this anabolic agent.

Recently we demonstrated that the administration of GH during hypocaloric intravenous feedings results in significant positive nitrogen balance in both normal individuals[1] and patients requiring parenteral nutrition.[2] The purpose of the present study was to investigate the mechanisms of these changes by quantifying the alterations in protein and energy metabolism and the hormonal environment associated with GH administration.

Materials and Methods

Subjects and Study Design

Eight paired studies were performed in four healthy male subjects (average age = 31 years, weight = 72.0 kg, body surface area = 1.89 m2). A detailed report on the experimental subjects and the screening studies has already been given.[1]

Each study consisted of two 7-day periods separated by at least 2 weeks. During the first period, the subjects

received daily injections of GH[1]*, 10 mg subcutaneously, at 8:30 a.m. daily, and during the second period, they received similar injections of saline, likewise administered daily at 8:30 a.m. The subjects were unaware of the contents of the injections.

During each 7-day period the subjects received all of their nutrients by parenteral infusion and were allowed distilled water only by mouth. The diets, which have been described in detail in an earlier report,[1] contained adequate electrolytes, trace elements, vitamins, and protein (6 gm of nitrogen/m^2/day, or approximately 1 gm of protein/kg body weight/day), but varied in total calorie content. Three different diets were designed, providing 100, 50 and 30% of energy requirements, respectively. The diet that provided adequate (i.e., 100%) calories supplied basal energy requirements plus an additional 25% to meet the caloric needs of hospital activity. The diets providing 50 and 30% of energy requirements (1100 and 750 kcal/day, respectively) contained the same quantity of protein as the adequate diet. In the adequate and 50% adequate diets, energy was provided through fat and carbohydrate; In the 30% diet, carbohydrate calories only were provided. Four paired studies were carried out with the diet that provided 50% of calorie requirements, and two paired studies were conducted, each with the 100% and 30% diets (Table 1).

At 6 a.m. on the final study day, the nutrient infusion was discontinued, and after a 5-hour fast, the response to a 100 g oral glucose load was determined.

Measurements

The subjects were weighed daily, and their vital signs were recorded every 4 hours. All urine and stool was collected, and the output for each 24-hour period (6 a.m.–6 a.m.) was pooled. Blood samples for insulin and glucose determination were drawn at 6 a.m. on Day 1 (before the infusion of nutrients), and Days 4 and 7 (while the nutrients were being infused). Samples were drawn for GH determination at 12:30 p.m. on Days 1, 4, and 6. Insulin and GH were measured by a double radioimmunoassay technique.[3]

Blood samples were also obtained at 6 a.m. on Day 1 and at 12:30 p.m. on Day 6 for measurements of IGF-I (insulin-like growth factor I/somadomedin C). EDTA-treated plasma samples were extracted with acid-ethanol,[4] and IGF-I was measured using a double antibody method.[5]

Blood was drawn for estimation of serum amino acids at 6 a.m. on Day 1 (before the initiation of the nutrient infusion) and at 6 a.m. on Day 7 (before stopping the infusion). Samples were assayed on a Beckman 6300 amino acid analyzer using Ninhydrin™ technology (Beckman Instruments, Fullerton, CA). Glutamine and glutamic acid were determined separately by an enzymatic method.[6]

TABLE 1. *Dietary Intake and Number of Subjects Studied*

Diet	Mean Calorie Intake Kcal/m^2/day	Number of Subjects Studied* Control	GH
Adequate (100%)	1155	2	2
50% Adequate	566	4	4
30% Adequate	398	2	2

* Each subject was studied in the control and treatment arms.

The 24-hour urine samples were analyzed for total nitrogen, using the macro-Kjeldahl method. Samples of the intravenous fluids were analyzed by the same method to quantitate nitrogen intake. Urine collected on the last 3 days of each study period was analyzed for 3-methylhistidine by high pressure liquid chromatography.[7]

Nitrogen turnover, synthesis, and catabolism were determined using the method described by Picou and Taylor-Roberts,[8] as previously described.[9] 15N-glycine™ (Cambridge Isotope Laboratories, Cambridge, MA) was administered orally every 3 hours on Days 4–7, and 3-hour urine samples were collected on Day 7. The enrichment of urine urea was determined by an isotope ratio mass spectrometer (Nuclide Corp., State College, PA). Nitrogen turnover was calculated and this value, together with known nitrogen intake and excretion rates, was used to calculate protein synthesis and catabolism.

At 6 a.m. on the 7th day of each study period, the nutrient infusion was discontinued, and at 8:30, an additional injection of GH or saline was given. Between 10:15 and 10:30 a.m., a catheter was positioned in retrograde direction in an antecubital vein for sampling of blood from forearm musculature. A second catheter was inserted in a contralateral dorsal hand vein, and the hand was placed in a heating pad.[9] After a 30-minute rest period, samples of deep venous and arterialized blood were obtained simultaneously for analysis of whole blood glucose, amino acids, lactate, serum-free fatty acids, and glycerol.[9] Blood flow was then measured by venous occlusion capacitance plethysmography.[9] At 11 a.m., a 100 g oral glucose load was given (as Glucola™), and sampling of arterial and venous blood, as well as measurements of forearm blood flow, were made at 30- and 60-minute intervals. The same arm was used for each portion of the paired study.

* given as Asellcrin™ (Serono Pharmaceuticles Ltd., Randolph, MA) or Protropin™ (Genentech Inc., San Francisco, CA)

TABLE 2. *The Effect of GH on Nitrogen Balance and Nitrogen Kinetics (mean ± SEM, g or μmol/m²/day)*

	Control	GH
Nitrogen intake (g)	6.0 ± 0.1	6.0 ± 0.1
Nitrogen excretion (g)	7.3 ± 0.3	5.0 ± 0.2†
Nitrogen balance (g)	−1.2 ± 0.3	1.0 ± 0.3†
Nitrogen turnover (g)	21.5 ± 0.9	22.0 ± 0.8
Nitrogen synthesis (g)	13.9 ± 0.8	16.8 ± 0.7*
Nitrogen breakdown (g)	15.4 ± 0.8	15.9 ± 0.8
3-Methylhistidine excretion (μmol)	164 ± 16	172 ± 16

* $p < 0.01$.
† $p < 0.001$ by paired t test.

Gas exchange measurements were made using a Metabolic Measurement Cart™ (Beckman Instruments, Fullerton, CA) before the oral glucose load was given and every 30-minutes thereafter during the 4-hour duration of the study. When the gas exchange measurements and blood sampling occurred at the same time, gas exchange was performed first, and immediately afterwards, blood sampling and flow determinations were made.

Calculations

Statistical analysis was performed with a VAX 11/780 computer™ (Digital Equipment Corp., Maynard, MA) and a standard software package (Minitab 82.1, Penn State University, University Park, PA) using linear regression methods and paired t testing. Because growth hormone treatment exerted a much greater effect than the variation in calorie intake, using paired analysis, data from the different diets were combined and compared with the comparable control studies.

Daily balance was calculated as the difference between intake (amount in the nutrient fluid) and urine output. Stool samples, which were minimal and assumed to reflect oral food ingestion before the start of the parenteral feedings, were not included in the balance calculations. Average balance was calculated for each subject after exclusion of data from the first 24 hours as a lead-in period. The mean nitrogen balance thus represents the average for Days 2–6.

TABLE 3. *The Effect of Parenteral Nutrition and GH on Total and Selected Amino Acid Concentrations (mean ± SEM, μmol/L)*

	Control		GH	
	Day 1	Day 7	Day 1	Day 7
Total nitrogen	4523 ± 170	4940 ± 338	4710 ± 183	5049 ± 208
Alanine	298 ± 30	392 ± 36	350 ± 28	497 ± 30*
Glutamine	563 ± 23	541 ± 41	603 ± 52	573 ± 38
Leucine	129 ± 3	130 ± 4	128 ± 9	118 ± 6
Isoleucine	67 ± 3	83 ± 6*	68 ± 3	92 ± 5*
Valine	243 ± 5	273 ± 18	245 ± 6	272 ± 12

$p < 0.05$ when compared with Day 1 by paired t test.

The nitrogen content of each amino acid was calculated and the 22 amino acids summed to determine amino acid nitrogen concentration in arterial and venous blood samples. Forearm flux was determined as the product of the arteriovenous concentration difference and the forearm blood flow. Metabolic rate, fat oxidation, and carbohydrate oxidation rates were calculated from the oxygen consumption and carbon dioxide production data according to the equations of de Weir.[10]

The areas described by the glucose, insulin, and amino acid response curves after the oral glucose load were calculated by standard methods for determining areas of triangles and trapezoids, and were used to express the integrated response over time. The insulinogenic index was calculated as described by Seltzer.[11] The values derived from the forearm studies were adjusted for the whole body muscle mass as described by Andres et al[12] and using the predictions of whole body muscle mass determined by Cohn et al.[13]

The mass of glucose in the glucose space above basal was calculated by subtracting the initial glucose concentration from the concentration at 240 minutes and then multiplying by the extracellular fluid volume (17 L in a man weighing 70 kg). The quantity of glucose stored was calculated by subtracting the glucose oxidized, excreted, and present in the glucose space from the 100 g glucose load, assuming 100% absorption.

Differences were considered significant if the p value was <0.05. All values are expressed as mean ± SEM.

Results

Nitrogen Kinetics

As a group, the subjects were in negative nitrogen balance throughout the control portion of the study (Table 2). With GH administration, nitrogen excretion was significantly diminished, and as a result, the subjects were in positive nitrogen balance. The difference in nitrogen balance between control and GH-treated subjects exceeded 4 g of nitrogen/day.

Nitrogen turnover, calculated from the N15 enrichment of urinary urea nitrogen, was similar in both the control and GH periods (Table 2). However, the administration of GH was associated with a marked increase in protein synthesis (16.8 ± 0.7 *vs.* 13.9 ± 0.8 g/m²/day, $p < 0.01$). In contrast, the rate of protein breakdown was not significantly affected by GH administration. Excretion of 3-methylhistidine, a marker of myofibrillar protein breakdown, was also similar in both the control and GH treatment periods. Thus, two independent markers of protein catabolism, N15 turnover and 3-methylhistidine excretion, indicate that protein breakdown was un-

changed with GH therapy. As confirmed by the N15 data, GH must mediate its nitrogen-retaining effects by promoting protein synthesis.

Amino Acid Kinetics

Before the initiation of parenteral nutrition, serum amino acid concentrations were within the normal range and tended to increase slightly with the constant infusion of the amino acid-calorie mixture (Table 3). The increase in the serum concentration of amino acid nitrogen was similar in control and GH-treated subjects. Changes in specific amino acids, such as isoleucine, reflect the composition of the amino acid formula that was infused and are not attributed to the GH therapy or other experimental conditions. The alanine concentration tended to increase in the control group and rose significantly with GH therapy, but the magnitude of the response was not different between groups.

Basal forearm flux of amino acids was similar in the control and GH-treated subjects (−862 ± 258 *vs.* −1,234 ± 277 nmol/100 ml/min). Following the oral glucose load, forearm amino acid efflux tended to increase in the control studies and returned to basal levels with time. This response tended to be attenuated in the GH-treated subjects (Fig 1). Integration of the areas described by the amino acid response curves yielded values that approached, but did not achieve a significant difference between control and GH periods (−150,000 ± 105,000 *vs.* +67,000 ± 87,000, $p < 0.06$).

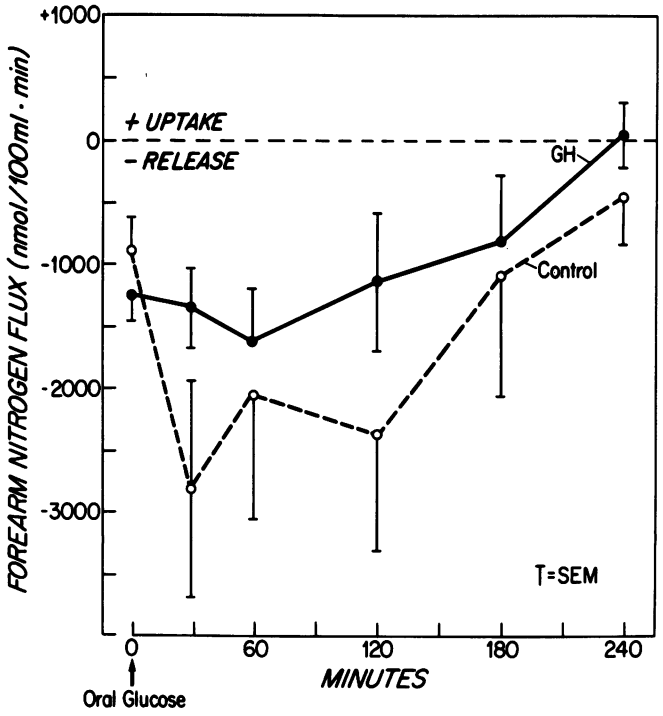

FIG. 1. The flux of amino acid nitrogen across the forearm was similar in the postabsorptive period (time 0) for the GH and control groups. However, following glucose ingestion, efflux increased (i.e., became more negative) in the controls, but this response was attenuated with GH.

Hormonal Response to GH

Glucose levels tended to rise with infusion of the parenteral nutrient solution (Table 4). Although there appeared to be a greater increase in glucose concentration in the subjects treated with GH, these levels did not rise significantly above the values obtained during the control period.

Insulin concentrations rose from the initial basal levels and remained stable throughout the infusion period in the control portion of the study. With GH administration, insulin levels were almost twice that of values observed in the control study, although this difference did not reach statistical significance (Table 4).

IGF-I levels were similar in the two groups at the start of the study and did not change during the time of the control infusion (Table 4). However, when the subjects received GH, the concentrations increased significantly —to almost three times the levels observed in the control study.

Effect of the Ingested Glucose Load

Five hours after discontinuation of the parenteral nutrition, serum substrate concentration and fuel utiliza-

TABLE 4. *Concentration of Glucose and Anabolic Hormones (mean ± SEM)*

Day of Study	Insulin (μU/ml)		Glucose (mg/dl)		IGF-I Free (IU/ml)		IGF-I Extracted (IU/ml)	
	Control	GH	Control	GH	Control	GH	Control	GH
1	11 ± 1	9 ± 1	85 ± 3	84 ± 3	0.67 ± 0.05	0.67 ± 0.05	2.2 ± 0.2	2.4 ± 0.2
Mean of Day 4–6	16 ± 4	37 ± 14	94 ± 4	108 ± 7				
6					0.91 ± 0.24	4.1 ± 0.3*	3.3 ± 0.5	9.1 ± 0.6†

* $p < 0.01$.

† $p < 0.001$ when compared to values obtained on day six by paired t test.

TABLE 5. *Serum Substrate, Hormone Concentrations and Fuel Oxidation on Day 7 (expressed as mean ± SEM)*

	Control	GH
Glucose (mg/dl)	74 ± 4	79 ± 4*
Insulin (μU/ml)	8 ± 1	28 ± 11
GH (ng/ml)	3.2 ± 1.0	33 ± 7†
Free fatty acids (μeq/L)	924 ± 41	1114 ± 91*
Glycerol (mg/dl)	1.28 ± 0.14	1.71 ± 0.06*
Acetoacetate (mmol/L)	0.13 ± 0.03	0.11 ± 0.03
B-hydroxybutyrate (mmol/L)	0.32 ± 0.12	0.20 ± 0.05
Lactate (mmol/L)	0.83 ± 0.08	0.90 ± 0.05
Carbohydrate oxidation (g/m^2/24 hr)	46 ± 12	44 ± 145
Fat oxidation (g/m^2/24 hr)	43 ± 5	59 ± 4*

* $p < 0.05$.
† $p < 0.001$ when compared to control value by paired t test.

tion varied between the two groups; glucose, free fatty acids, and glycerol increased in the subjects receiving GH, compared with the controls (Table 5). In addition, fat oxidation was greater in the GH-treatment period than in the control period (59 ± 4 g/m^2/24 hr *vs.* 43 ± 5, $p < 0.05$).

After ingestion of 100 g of glucose, blood glucose increased approximately twofold in the controls and stimulated a brisk release of insulin (Table 6). When glucose was administered to subjects receiving GH, blood glucose tended to rise to higher levels and decreased in a more gradual manner (Fig 2). This diabetic-like response occurred even though insulin levels rose to more than twice what they were during the control period.

The insulinogenic index, which reflects the insulin response per unit glycemic stimulus, was increased when the subjects received GH (2.37 ± 0.30 *vs.* 1.26 ± 0.21, $p < 0.05$). Despite the increased elaboration of insulin, blood glucose attained greater levels at 120 and 180 minutes following GH treatment (Table 6) and remained elevated for a longer period after GH than saline. The rate constant for glucose disappearance was significantly reduced after GH. The slope of the line fitted from the peak to the trough of the glucose tolerance curves averaged 0.56 ± 0.03 mg/dl/min for the controls *vs.* 0.37 ± 0.07 for the GH-treated subjects ($p < 0.05$).

After glucose ingestion, forearm glucose uptake increased significantly (Table 6). However, the increase in forearm uptake was approximately 60% greater in the

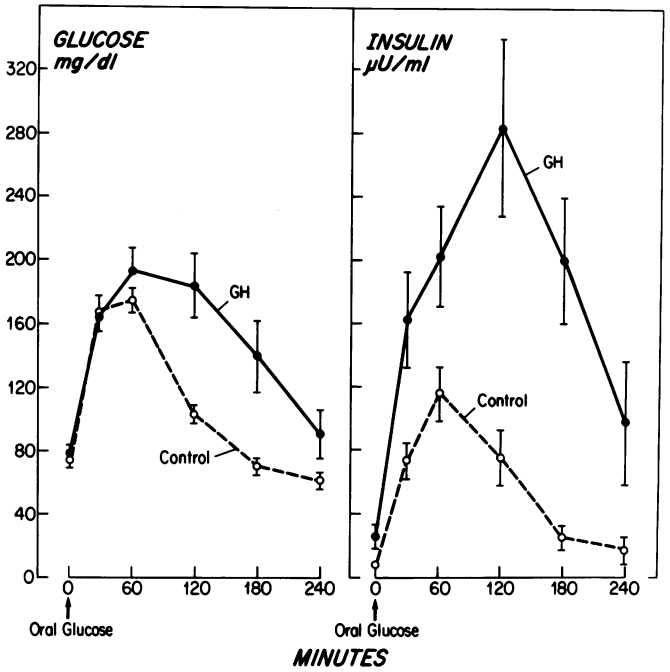

FIG. 2. Alterations in whole blood glucose and serum insulin occurred following GH. Despite the slight increase in peak blood glucose concentration and the prolonged rate of disappearance, at 120 minutes insulin rose to levels more than three times those of control concentrations. Despite this exaggerated insulin response, a mild state of insulin resistance occurred, as reflected in the diabetic-like glucose tolerance curve.

TABLE 6. *The Effect of a 100 g Glucose Load on Forearm Glucose Uptake and Hormonal Response (mean ± SEM)*

					Forearm Glucose Uptake					
					ARTERIAL VENOUS DIFFERENCE (mg/dl)					
	Glucose (mg/dl)		Insulin (μU/ml)				FLUX (mg/100ml/min)		GH (ng/ml)	
Time	Control	GH	Control	GH	Control	GH	Control	GH	Control	GH
0	74 ± 4	79 ± 4*	8 ± 1	28 ± 11	−2 ± 2	2 ± 2	−0.04 ± 0.02	0.04 ± 0.04	3.2 ± 1	33.7 ± 7‡
30	167 ± 9	164 ± 9	74 ± 12	161 ± 33†	16 ± 4	16 ± 4	0.52 ± 0.20	0.65 ± 0.11	0.8 ± 0.2	36 ± 6‡
60	175 ± 7	193 ± 14	113 ± 15	202 ± 30†	23 ± 5	13 ± 2*	1.03 ± 0.20	0.58 ± 0.09*	0.6 ± 0.1	34 ± 7‡
120	103 ± 5	184 ± 20†	74 ± 17	286 ± 52†	20 ± 4	11 ± 4	0.88 ± 0.20	0.58 ± 0.16	0.6 ± 0.1	33 ± 6‡
180	70 ± 5	139 ± 22†	24 ± 8	199 ± 40†	9 ± 4	11 ± 4	0.56 ± 0.20	0.45 ± 0.13	0.6 ± 0.1	32 ± 5‡
240	61 ± 5	90 ± 16	18 ± 10	95 ± 32	2 ± 2	4 ± 2	0.05 ± 0.04	0.13 ± 0.07	14.2 ± 5.1	30 ± 4†

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$ when compared with control by paired t test.

TABLE 7. *Gas Exchange Measurements During a 100 g Glucose Load*

TIME (mins)	Metabolic Rate Kcal/m²/24 hrs		Respiratory Quotient		Carbohydrate Oxidation g/m²/24 hrs		Fat Oxidation g/m²/24 hrs	
	Control	GH	Control	GH	Control	GH	Control	GH
0	775 ± 42	857 ± 46	0.79 ± 0.02	0.78 ± 0.02	46 ± 12	44 ± 15	43 ± 5	59 ± 4*
30	835 ± 39	937 ± 50	0.82 ± 0.02	0.79 ± 0.02	66 ± 17	65 ± 16	40 ± 7	58 ± 4*
60	853 ± 34	928 ± 49	0.86 ± 0.02	0.85 ± 0.03	98 ± 15	95 ± 20	28 ± 5	39 ± 7
90	879 ± 45	959 ± 56	0.90 ± 0.01	0.87 ± 0.03	130 ± 12	129 ± 28	17 ± 4	32 ± 9
120	871 ± 38	943 ± 62	0.92 ± 0.03	0.88 ± 0.02	138 ± 17	132 ± 23	13 ± 8	29 ± 7
150	851 ± 38	928 ± 51	0.93 ± 0.03	0.92 ± 0.02	148 ± 21	162 ± 24	6 ± 8	15 ± 7
180	837 ± 42	936 ± 52	0.94 ± 0.04	0.92 ± 0.02	150 ± 26	160 ± 21	10 ± 7	16 ± 8
210	825 ± 32	933 ± 62	0.88 ± 0.02	0.95 ± 0.03‡	106 ± 17	184 ± 33†	21 ± 7	5 ± 10†
240	832 ± 48	876 ± 52	0.81 ± 0.02	0.88 ± 0.03*	55 ± 28	122 ± 25‡	44 ± 8	26 ± 8†

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$ when compared with control by paired t test.

control *versus* GH study periods. The integrated area described by the forearm glucose uptake curve was 1.64 ± 0.30 g/kg forearm in the controls *vs.* 1.10 ± 0.19 following GH ($p < 0.05$). Despite marked hyperinsulinemia, the decrease in glucose uptake by forearm muscle was indicative of insulin resistance in skeletal muscle with GH therapy.

Following carbohydrate ingestion, metabolic rate and the respiratory quotient increased slightly (Table 7), and this rise tended to be greater in the GH treated subjects than in controls. Fat oxidation was greater with GH treatment at the beginning of the study, but decreased as the study progressed. This attenuation in fat utilization occurred as carbohydrate oxidation increased; both alterations were related in time to the marked hyperinsulinemia associated with GH. The calculated distribution of the 100 g glucose load revealed that after GH treatment, less carbohydrate was stored and total muscle uptake was reduced (Table 8).

Discussion

Marked positive nitrogen balance and accelerated protein synthesis occurred in normal volunteers given GH along with adequate or hypocaloric feedings and amino acid infusions. A similar response has been observed after GH was administered to adequately nourished but GH-deficient patients.[14] The nitrogen retention reflects increased protein synthesis, which occurs throughout the tissues of the body. Because skeletal muscle represents the largest mass of protein-containing tissue, the hormonal effect is particularly evident in skeletal muscle. As we have previously reported, the retention of nitrogen and minerals in GH-treated subjects is similar to the composition found in skeletal muscle.[1]

Positive nitrogen balance in our subjects could have resulted from an increase in protein synthesis, a decrease in protein breakdown, or a combination of these responses. The N15 isotopic studies and the 3-methylhistidine excretion data indicate that protein breakdown was unaltered and that the positive nitrogen balance resulted solely from increased protein synthesis. This is consistent with previous studies of protein kinetics in postoperative patients given GH and I.V. dextrose,[15] and with animal and *in vitro* data showing both increased RNA generation and accelerated protein synthesis in response to GH.[16]

In addition to retention of nitrogen and decreased urea generation, a fall in plasma amino acids after GH administration has also been observed.[16] This was not seen in our subjects, however, possibly because they were adequately nourished and given constant infusion of moderate quantities of I.V. amino acids. In the postabsorptive state, no difference in forearm amino acid flux was detected when data from the control and GH periods were compared. This observation is not inconsistent with studies in fasting obese subjects, where GH failed to promote nitrogen sparing.[17] Alternatively, the forearm amino acid balance technique may not be sensitive enough to detect small differences in nitrogen flux, as Bessey et al. have discussed in detail.[18]

After administration of an oral glucose load, two different patterns of forearm amino acid flux appeared to occur. In GH-treated subjects, the forearm tended to retain amino acids, whereas the forearm of control subjects generally lost amino acid nitrogen. This retention

TABLE 8. *Fate of 100 g of Ingested Glucose (expressed as g, mean ± SEM)*

	Control	Growth Hormone
Oxidized	20.6 ± 1.7	24.4 ± 2.7
Stored	79.0 ± 1.6	69.7 ± 3.2*
In glucose space	0.3 ± 0.3	4.4 ± 2.9
Urinary loss	0.1 ± 0.1	1.8 ± 1.0
Taken up by muscle	48.8 ± 8.7	32.9 ± 5.3*
Nonmuscle disposal	51.2 ± 8.7	67.1 ± 5.3*

* $p < 0.05$ when compared with control values by paired t test.

of amino acids may be a response to the increase in levels of insulin that occur after the administration of GH. Additional flux studies will be required in order to document muscle uptake at the time parenteral nutrients are being infused.

The hormonal and metabolic mechanisms that lead to increased protein synthesis after GH administration are complex, multiple, and probably interactive. GH is known to stimulate the synthesis and secretion of IGF-I by the liver, and it is thought that IGF-I mediates the anabolic actions of GH in many tissues.[19] In the present study, IGF-I levels in the circulation were increased three- to fourfold after GH, and this is consistent with this proposed mechanism of action. Alternatively, GH has been shown to have direct effects on protein synthesis in certain cells and perfused organs independent of IGF-I of other somatomedins.[16] It has also been recently found that IGF-I can be secreted locally, near or in tissues affected by GH.[20] It is possible that local IGF-I secretion could occur in response to GH (at least in some tissues), and then IGF-I could act in a paracrine or autocrine manner to mediate the anabolic effects of GH. Finally, other factors such as the accelerated mobilization and utilization of lipids, especially by skeletal muscle, could also exert significant protein-conserving effects.[21] Thus, GH administration can stimulate protein synthesis through a combination of several different mechanisms. Although the current study does not allow us to define the contributions of the individual factors on the accretion of body protein, it is clear that GH administration results in a hormonal-substrate environment that markedly favors nitrogen retention and protein synthesis.

In summary, humans given GH achieve positive nitrogen balance while receiving either adequate or hypocaloric parenteral nutrition. The clinical use of GH along with hypocaloric feedings may reduce the need for the infusion of large quantities of calories, which had previously been necessary to attain positive nitrogen balance and tissue repair. The positive nitrogen balance that occurred in these normal individuals was the result of accelerated protein synthesis, not diminished protein degradation. Increased protein synthesis occurred simultaneously with elevation of GH concentrations, hyperinsulinemia, increased IGF-I levels, and accelerated fat mobilization. All of these factors may have contributed to accelerated body protein synthesis. GH administration was associated with marked insulin resistance and hyperinsulinemia, although because of the relatively small amount of glucose that was present in the hypocaloric diets (300 g/day), glucose intolerance was not observed. This quantity of glucose is sufficient to supply obligate glucose requirements, but not enough to produce hyperglycemia.

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